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(An Undergraduate Publication)

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EDITORIAL.

DISCUSSION GROUPS.

Among the editorials we published last spring was one on discussion groups. As it appeared so late in the academic year and as the subject is, we feel, of considerable interest to our readers, some portions of it are republished here.

All medical students know from experience what an excellent hypnotic it is to sit down and read a textbook's dogmatic, bald statements. A method of having our interest in medical matters stimulated more frequently and thoroughly is by taking part in a discussion group. In preparing a paper or in hearing one read, we find what a living, growing body of knowledge it is with which we are dealing---a very different picture from the valley of dry bones presented by the textbooks.

Very few of us are able by ourselves to overcome our starting inertia and to read beyond our textbooks and lecture notes; but with the stimulus of a group of fellow students many of us would do so. Again, we haven't the time to dig deeply into more than a very few subjects; in such a group, however, a considerable variety of subjects may be covered very effectively throughout the year.

The experience in discussion groups in preparing, presenting and defending papers will stand many of us in good stead in after years in fulfilling a similar function at association meetings and in journals. Edinburgh has produced many famous speakers and writers on medical subjects, and credit is given there to the discussion groups which have been in existence for years.

A few practical suggestions on the conduct of such a group may be in order. The group should not be too large, certainly not over twenty in number, twelve is much preferable—for the sake of informality and freedom of discussion. The meetings should be frequent, at least fortnightly. It is well to invite one or two staff members to each meeting to assist in the discussion. As a diversion, an occasional meeting may be given over to an outstanding character in medical history. In this connection, Cushing in his "Life of Sir William Osler" presents a very attractive picture of the Saturday nights at Osler's house in Baltimore where a group of a dozen or so students would gather around the dining-room table while Osler himself or one of the students gave a paper on some ancient medical worthy, which was then discussed over beer and crackers and cheese.

Several discussion groups should be formed in each year. The Journal will be pleased to publish for the benefit of all of us the pre-eminent papers that are presented in such groups.

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ARTICLES FOR THE JOURNAL.

There are two types of articles by the publication of which this Journal may be particularly useful to the undergradutes. One is the discussion of a symptom along the lines which a practitioner would follow in reaching a provisional diagnosis. The other is a review of recent literature bringing our knowledge of a subject right up to date. We have secured several papers along these lines from members of the staff, and these will appear in the remaining numbers of this volume. We will give a particular welcome to articles of similar plan from undergraduates.

From experience in reading articles, we would like to make a few suggestions to our contributors.

1. Subjects chosen to apply to common, rather than rare, conditions.
2. Subjects to be discussed from standpoint of practising physician.
3. Recent significant experimental work to be included as far as possible.
4. History and etiology to be brief, except where etiology has reached a stage of knowledge when diagnosis and treatment are definitely influenced.
5. Statistics to be used sparingly, and stated in a striking manner.
6. Diagnosis to be given as on a patient seen for the first time—not a textbook picture—rather along deductive lines than as routine history and examination.
7. Treatment to have experimental, physiological, and anatomical backgrounds.

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Articles submitted should be typed and in shape to go to the printer. Common grammatical errors are surprisingly common, and it would simplify the editorial work considerably if these were avoided; for example, see that the subject and the verb agree in number. Put in definite and indefinite articles (the a, and an) where needed. Do not use abbreviations.

We hope these observations will be received in the spirit in which they are meant. We will be very glad to receive undergraduate articles, or to be consulted about such.

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As the oldest (we believe) of the undergraduate medical journals on this continent, we welcome, this month, with the appearance of its first number, the fourth of the family, the University of Western Ontario Medical Journal. It is a rather large child, being sixty pages in length, and containing thirteen articles, forewords by the President of the University and the Dean of the Medical Faculty, an editorial and book reviews—altogether a very excellent start in life. It is to be published quarterly by the University of Western Ontario Medical Society, and is edited by undergraduates with the assistance of staff advisers. We wish the University of Western Ontario Medical Journal every success.

The Examination of the Nervous System.

By H. H. HYLAND, M.D.

It is essential in the examination of the nervous system that a systematic procedure is used which will be employed fully on every neurological patient. Unless the system of examination is firmly fixed in the mind of the examiner much time will be wasted and important points missed.

The actual order of examination is not of great importance and may be left to the discretion of the individual, but whatever order is adopted should be followed faithfully in every case. If this is done it is unlikely that omissions will occur.

The following is a brief outline of a system of examination containing the minimum necessary for a satisfactory investigation of the nervous system.

General Impression of the Patient.

The attitude of the limbs and the head are observed, the presence of involuntary movements (choreiform, athetotic, tremors, etc.); the expression of the face (immobility, grimacing, tabetic mask etc.).

Higher Mental Functions.

Is coma or delirium present? Is the patient unduly drowsy? Is he attentive or does his mind wander? Is he negatavistic or unduly suggestible? Is he co-operative? Is orientation good in space and time? Is the memory good for recent and remote events? Is he euphoric or unduly depressed? Is there flight of ideas or retardation of thought? Question carefully for delusions or hallucinations.

If there is reason to suspect mental impairment, ask question in mental arithmetic and submit questions of current interest. The answers will indicate defects in perception and judgment which may be present.

From the above examination an impression may be gained of the patient's mental status. More detailed examination will be necessary if there is reason to suspect a psychosis or gross mental impairment.

If spontaneous speech is affected the possibility of dysarthria, or aphasia, must be considered.

Dysarthria (articulatory disturbance) is made more apparent when the patient repeats test phrases, e.g., "Truly rural," "British constitution," etc. If the muscles and peripheral nerves of the articulatory mechanism are intact, dysarthria is due either to disease of the pyramidal system (as in G.P.I.) or of the cerebellum (as in disseminate sclerosis) slurring, omission of syllables, reduplication of syllables will be noted.

Aphasia (non-articulatory disturbance) must be clearly distinguished from dysarthria. The articulatory mechanism is intact but the exteriorization and comprehension of written and spoken speech are affected.

A useful routine method for examining aphasic patients follows:

Is the patient right or left handed? What education has he had previously? Does he understand the nature and use of common objects? Can he understand gestures? e.g., make a movement as if to strike him and note his reaction. Is his hearing intact,—if not how much disturbed? Can he recognize ordinary sounds and noises? Can he comprehend spoken language? e.g., does he obey commands at once—what mistakes? What is the natrue of spontaneous speech? Does he omit words, use wrong words, mutilate words, construct his sentences faultily or talk jargon? Is perseveration of speech present? e.g., does he continue repeating one phrase or sentence in answer to several different questions? Can he repeat words uttered in his hearing?

Test automatic speech by having patient say the Lord's Prayer or the alphabet, etc.

Be sure the eyesight permits reading and then test ability to comprehend written speech. Can he obey written commands? Does he recognize words, letters or numerals? Can he write spontaneously — what mistakes? Can he copy written words or write from dictation? Can he perform simple written arithmetic problems? Can he read aloud? What mistakes? Does he understand what he needs? Can he name at sight common objects? When several objects are presented to him can he match each one with its name spoken or written? Can he still play cards or play a musical instrument?

Test the patient for apraxia by handing him familiar objects, e.g., tooth brush, match and cigarette, telephone, etc.

When the results of this examination are all before the examiner he must carefully decide the character and degree of the aphasia present. In all aphasias the speech function is depressed as a whole and there is a general lowering of the higher mental faculties, but it is important to know if the aphasia is mostly motor, or mostly sensory, if word blindness is present or word deafness, etc. The examination should never be done at one sitting, but on several occasions because aphasics tire quickly and the aphasia often varies from day to day.

Cranial Nerves.

Olfactory Nerve.

Only those substances are appreciated which are readily oxidizable, therefore only the essential oils should be used in testing, e.g., oil of cloves, oil of wintergreen, etc.

Test each nostril separately and remember that there is a large normal variation between individuals in the keenness of sense of smell.

Unilateral anosmia is more important than bilateral—the latter may be produced by several local and general diseases.

If anosmia is found it is usually of value to determine that the 5th nerve is intact and that the anosmia is not due to an atrophic process in the mucous membrane. This is done by observing the reaction of the patient when told to inhale spirit of ammonia on the affected side. If the reaction is normal it indicates that the anosmia is due to a lesion of the olfactory nerve.

Optic Nerve.

Acuity of vision. This must be tested in all neurological cases using Snellin's charts. It is done without glasses (uncorrected) and with glasses (corrected) and the results charted.

Visual fields.—The rough test is usually employed. The right eye of the patient is fixed by the left eye of the examiner and the other eyes closed. A small round white object should be used and brought in from the periphery by the examiner from all angles. If the patient's field is more restricted than the examiner's the test must be repeated accurately by using a perimeter. The other eye is examined in the same fashion.

Certain patients are unable to cooperate in this test, and it may be of the greatest importance to determine if a field defect is present. In these cases if the examiner stands behind the patient while someone endeavors to attract attention in front, threatening movements in view of the temporal fields on each side may indicate the side of the defect by the absence of the blinking reflex.

The most important field defects to be recognized are right or left homonymous hemianopias, bitemporal hemianapias and quadrantic field defects.

Scotomata—can be readily tested by emplaying a small white object attached to a long stalk. The old-fashioned hat pin with a head as large as a pea is satisfactory. The eye of the patient is fixed as in testing the visual field and the object slowly moved from the point of central vision towards the periphery in all directions. The examiner measures his own blind spot against the patient's and any increase in size of the patient's blind spot is noted. Time and care are necessary in getting results and the co-operation of the patient is necessary. Colored objects should be used in addition to white—red and green are the most important. In retrobubar neuritis a central colour scotoma is one of the earliest signs.

Ophthalmoscopic Examination.

In the retina the most important observations from a neurological standpoint are changes in the macula (e.g. cherry red spot in amaurotic family idiocy), vascular abnormalities (e.g. haemorrhage, arteriosclerosis), and syphilitic choroiditis.

In the examination of the fundus we look for papilloedema and often atrophy. Papilloedema, if well marked, is easy to recognize, but the very early changes are often overlooked. It is well to remember that the nasal side of the disc is the first to show change it becomes less distinct and the whole disc becomes increasingly red with disappearance of the physiological cup.

Vision may be perfect with high degrees of papilleodema present, particularly if the latter is of acute onset. When papilloedema has been present for some time, however, optic atrophy commences and visual failure occurs proportionately.

Optic Atrophy may be divided into 3 types: (1) primary, (2) secondary, (3) consecutive.

(1) Primary is due to original devitilization and death of the nerve cells in the retina—the disc is pure white and flat, the vessels are small, the lamina cribrosa is plain, the edges of the disc are sharply cut.

(2) Secondary—results from lesions of the optic chiasma or the optic nerve—the disc may exactly resemble that found in primary optic atrophy or some slight irregularity of the margins may be present.

(3) Consecutive—follows severe papilloedema. The disc is white and flat but the edges are fluffy and irregular.

Oculomotor Nerves (3, 4 & 6).

Ptosis, if present, will be noted first. A true ptosis must be distinguished from a "pseudoptosis" due to lesion of the cervical sympathetic causing of paralysis of the involuntary component of levator muscle. The latter produces a narrowing of the palpebral aperture on the affected side, but the upper lid does not cover the pupil when the patient looks directly in front.

Enopthalmos and exophthalmos are looked for

Eye movements are next observed. The eyes are examined at rest and any strabismus noted. Then the patient is requested to follow an object with his eyes, keeping his head motionless. The object is moved to the extreme right and left and up and down. If a strabismus is present but no double vision occurs (visual acuity being good in both eyes) it can be assumed that the ocular paralysis is of long standing and that the patient has learned to suppress the image seen by one of the eyes. If diplopia occurs in the presence of a well marked squint, slight or not recognizable, it can be assumed that the affected eye is the one on the same side as the diplopia. A red glass is placed over one eye and a light moved around through the field of vision. When diplopia occurs the position of the red and white images is noted. If the red image is on the opposite side to the covered eye (the white image will be similarly situated in relation to the uncovered eye) a crossed diplopia is present. If the red image is on the same side as the covered eye the diplopia is uncrossed. Crossed diplopia occurs with divergent strabismus, uncrossed with convergent strabismus. As the object is moved about the relative positions of the images are noted. With a knowledge of the functions of the ocular muscles it can be concluded which are at fault.

We have been considering the effect of peripheral impairment of ocular movement, but mention must be made of defects in conjugate deviation of the eyes which occur with supranuclear lesions of the oculomotor nerves.

Paralysis of conjugate deviation is not in terms of muscles but of movements. Thus you may see paralysis of upward movements of the eyes, paralysis of convergence paralysis of lateral movements to the right, or left, and paralysis of downward movement. There is no strabismus or diplopia with defects in conjugate deviation, and it is important to distinguish this type of ocular paralysis from that resulting from disease of the oculomotor nerves of the lower motor neurone type.

The pupils are examined in regard to size, inequality, shape, contour, reactions to light, direct and consensual, and reaction to accommodation.

In testing for light it is important to always use the same strength of illumination thus providing a standard in judging sluggishness of pupils. It is necessary always to fix accommodation, preferably on some distant object, before throwing light into the pupil.

Nystagmus will be seen if present when the eyes are at rest. The patient follows an object with his eyes to the right and to the left. If nystagmus occurs on lateral deviation to the right or left or both, note its character and rate. It is usually horizontal but may be vertical or rotatory. It may be coarse or fine, slow or rapid.

True nystagmus is well sustained and lasts indefinitely. This must be distinguished from nystagmoid jerks, which are usually of little significance and can be obtained in many people if the lateral deviation is very extreme or the patient tired.

Trigeminal Nerve.

Motor division. The patient is asked to open his mouth against resistance. Any deviation of the jaw is noted; if the relative position of the front teeth is observed before the patient opens his mouth the examiner will not be deceived in the event of a facial palsy being present also.

In paralysis of the motor division the jaw deviates to the side of the lesion. The muscles on the floor of the mouth fail to harden on the side of the lesion. The patient is asked to bite and the anterior edges of the masseter muscles are felt at the time of the movement. The temporal muscles are also felt and any weakness in temporals or masseters will be readily detected as the jaws meet.

If the patient moves his lower jaw sideways with the mouth open there will be diminished excursion to the opposite side if a lesion is present.

Sensory Division. The corneal reflexes are tested with a horsehair after ascertaining that both obiculares oculi are functioning well. A difference on the two sides may be of great importance.

Sensation is tested over the area supplied by the three sensory divisions of the nerve, using cotton wool, heat and cold, and pin prick.

N.B.—In Tic Douloureux no sensory loss is present but the skin over the area of pain may be hyperaesthetic and tender points will be found where the main branches come close to the surface.

Facial Nerve.

Any asymmetry of the face is noted while at rest. The patient is asked to show his teeth and any failure of the two sides of the mouth to move out equally is observed. Just as important is an asymmetry in the furrows extending from the lateral borders of the nose.

In slight facial weakness the mouth may be drawn out well on the affected side but the corner of the mouth will not be elevated properly and will be on a lower horizontal plane than its fellow on the opposite side. The furrow will be less prominent and shallower on the weak side.

The patient is asked to "screw his eyes up tight" and not let the examiner open them. A weakness in the orbicularis oculi is readily detected by this means.

Additional information may be obtained by asking the patient to frown, wrinkle his forehead, whistle and blow out his cheeks.

The effect of emotional movement must then be observed, e.g., smiling, etc.

In lower motor neurone paralysis all movements are affected, voluntary and involuntary, the upper and lower part of the face are equally paralyzed on the side of the lesion.

In upper motor neurone paralysis the lower part of the face is much more affected than the upper part and involuntary movements, e.g., smiling, show no weakness.

In thalamic lesions involuntary movements only are affected, voluntary movements being normally performed.

In lower motor neurone lesions the sense of taste on the anterior two-thirds of the tongue should be tested. It is lost in lesions peripheral to the geniculate ganglion, the chorda tympani being involved in the lesion.

To test taste the tongue is protruded and dried. Minute quantities of salt, sugar, vinegar and quinine are placed on the affected side of the tongue with an applicator. After each substance is placed on the tongue it is wiped off before the patient puts his tongue in his mouth, otherwise the substance will pass to the normal side and the patient's statement will be valueless.

Auditory Nerve.

Cochlear division. One may test hearing with a watch, doing each ear separately and keeping closed the external auditory meatus of the ear not being tested. One must know what to normally expect with the watch that is used and the test must be performed in a quiet place.

The most important finding is a difference on the two sides and if this is found otoscopy should always be done.

If deafness is present it should be determined whether it is due to a lesion of the cochlear nerve or to middle ear disease.

Prinne's Test: A vibrating tuning fork is applied to the mastoid process on the effected side. When the patient ceases to hear it in that position the vibrating end is held close to the ear. In nerve deafness the hearing by air conduction and bone conduction is completely lost or else the patient hears by air conduction after he has ceased to hear by bone conduction. In middle ear deafness hearing by bone conduction lasts long after it has ceased to be audible by ear.

Weber's test: A tuning fork is applied to the centre of the forehead. In middle ear disease the sound is heard best on the deaf side. In nerve deafness it is heard best on the sound side.

Vestibular Division. Lesions of this division produce symptoms almost identical with those of cerebellar disease. Nerve deafness is always present, however, and the cerebellar symptoms are only seen in vestibular lesions when the condition is acute.

Vestibular functions are examined by the galvanic test, Barany's caloric test and the rotating test. Normally, following these tests, nystagnus deviation of the eyes and "past-pointing" occur; but if the vestibular mechanism is at fault the normal response is altered.

Glossopharynegeal and Vagus Nerves.

These nerves are considered together because their functions cannot be clearly separated.

The patient is asked to open his mouth and the palate is observed. If a lesion be present the palate may be seen to hang lower on the affected side. When the patient says "Ah" the palate moves up towards the non-paralyzed side. In bilateral lesions it will not move at all.

Sensation of the palate and pharynx should be tested. In unilateral lesions there will be anaesthesia of the palate and pharynx on the affected side, as shown by the absence of reflexes when the parts are ticked.

Difficulty in swallowing is never severe unless the lesion is bilateral but a moderate difficulty may be present with unilateral lesions more marked for fluids and solids.

The condition of the voice is noted, particularly a nasal tone, hoarseness or stridor. The larynx should always be examined if any evidence of paralysis of the tenth nerve is present whether changes in the voice are present or not.

Spinal Accessory Nerve.

Note whether any winging is present at the angle of the scapula.

The patient is asked to shrug the shoulders against resistance and any difference on the two sides is noted.

If doubt exists several other tests for the trapezii may be used, e.g., approximating the scapulae behind, and carrying the extended arm backwards.

The sternomastoids are tested by having the patient turn his head to the right and left while the examiner offers resistance with one hand and palpates the contracting muscles with the other. The affected muscle does not harden when the head turns to the side opposite the lesion.

Hypoglossal Nerve.

The patient is asked to protrude the tongue. In the presence of a unilateral lesion the tongue will deviate to the paralyzed side, being pushed over by the healthy muscles.

Atrophy may be seen on the affected side; the tongue is smaller and the mucous membrane has a crenated or wrinkled appearance on that side. In advanced atrophy the tongue is sickle-shaped.

In bilateral lesions (bulbar) fibrillation may be seen in the atrophied muscles.

Motor System.

Head and neck—the position of the head and any wasting of the muscles is noted. Passive movements and active movements against resistance are tried and any limitation or weakness observed.

Upper limbs—the following points are observed:

(1) Position of limbs at rest.

(2) Wasting — if present is it confined to muscle groups or is it generalized? The small muscles of the hands and the muscles of the shoulder girdles are the first to show wasting as a rule. If wasting is present look for fibrillation.

(3) Muscle power—the power is tested at all joints; the patient is told to perform the given movement against resistance and any weakness or inequality on the two sides noted. He is then told to hold the joints immobile and resist the examiner's attempt at movement.

Any difference in the grip of the two hands is noted. Normally the right hand will be a little stronger than the left if the patient is right handed; a dynamometer should always be used. If any indications are present the power in the fingers must be tested separately for flexion and extension at all joints and in abduction and adduction.

(4) Passive movement is tested at all joints and any limitation of movement or alterations in tone noted.

(a) Hypertonea—before concluding that tone is increased flexion and extension must be repeated several times (requesting the patient to relax) in order to rule out any voluntary element. If the limb is persistently hyper it must be decided whether it is pyramidal (hemiplegin) or extra-pyramidal (parkinsonism) in type.

If the latter it is equally present through the whole range of movement and probably accompanied by the cogwheel sensation. If the former, it is of the clasp-knife variety and much more marked on attempting extension than flexion.

(b) Hypotonia is often difficult to determine. If increased mobility is present in the joints and the limbs can be placed in abnormal positions it is easy, but in early cases this is not so.

Several useful tests are available for detecting hypotonin.

Stand behind the patient supporting his outstretched arms with your hands and give the arms little throws upwards. The hypotonic arm falls more heavily on the hands.

Hold the patient's hand with the arm flexed at the elbow and tell him to pull hard; suddenly let go his hand and if the arm is hypotonic his hand will not do so. This test is rather brutal but very satisfactory.

Ask the patient to relax his arm and suddenly throw it at his face — if the arm is hypotonic he will not stop it in time and it strikes the face. The normal arm will not do so.

(5) Involuntary Movements. Any choreic or athetoid movements or tremors at rest will have been noted. Certain tremors are present at rest and abolished by movement (e.g., paralysis agitans) other tremors only appear on movement (e.g. disseminate sclerosis).

(6) Co-ordination — severe inco-ordination will be obvious without special testing. The patient has difficulty in picking up objects, in buttoning his clothes and in feeding himself with the affected hand. Two tests are used to demonstrate the disturbance.

Finger-nose test. With the eyes open the patient is asked to touch the tip of his nose with the forefinger of the affected hand. It is important that the patient's arm is free from support during this test and that the elbow does not touch the bed. The movement should be performed slowly. Inco-ordination is recognized by the hand deviating in an uncertain fashion from the direct course to the nose and the finger strikes the face or the bridge of the nose. This test is also useful to demonstrate intention tremor. In early cures this will be seen at the end of the movement and the finger after striking the nose slips off or it may flatten the nose several times before coming to rest. Well marked cases of intention tremor show themselves earlier in the movement and increase as the objective is approached.

After the test has been performed with the eyes open it is permissable to have it done with the eyes closed, but it must be remembered that this introduces a new element, e.g., sense of passive movement.

Finger-nose-finger test — the examiner holds his finger up and the patient touches it with his forefinger and then touches his nose, repeating the movement several times with the eyes open. This is a more delicate test than the former, both for inco-ordination and intention tremor.

The Trunk. Look for any wasting of the muscles of the trunk. Bend the trunk forward, backwards and to each side and note any limitation of movement.

Ask the patient to sit up without using his hands and note how well he does it.

Lower Limbs. The motor functions are tested as in the upper limbs.

(1) Position of limbs at rest.

(2) Wasting, generalized or local.

(3) Power in all joints—on active movement and resisting movement.

(4) Tone.

(5) Co-ordination. Heel-toe test. Toe-finger test. The examiner holds out his finger some distance above the patient's foot. The latter endeavors to touch it with his great toe, raising the foot from the bed. When inco-ordination is present the foot describes wide arcs in the attempt of the toe to reach its objective.

(6) Involuntary movements.

Gait.

This is the most important part of the examination. The movements of the arms must be carefully watched. A hypotonic arm will not be swung as well as the normal arm. A hypertonic arm will likewise fail to move normally; in paralysis agitans the movements of the arms while walking suffer the same fate as many other "associated" movements in this disease and are diminished or absent.

The gaits characteristic of many neurological diseases must be seen and studied. e.g., spastic, ataxic, steppage, scissors, propulsive, etc. The hysterical gait is too grotesque to be mistaken for anything else.

Rhomberg's sign is tested, first with the eyes open and later with them closed.

Reflexes.

The following deep reflexes are tested as a routine: biceps, triceps, supinators, quadriceps and achilles.

The superficial reflexes to be tested in addition to those already mentioned are the plantars, abdominals and cremasterics.

The attempt is made to elicit ankle and patellar clonus. The organic reflexes are investigated: Bladder — is there difficulty in starting the flow, urgency, precipitancy or incontinence? can the patient hold his water too well? Bowels—is there incontinence or severe constipation?

Sensory System.

The sensations of light touch, heat and cold, and pain must be tested over the entire body surface. These sensations should not all be tested at one examination in detail if sensory loss is present, because patients tire quickly and their answers become unreliable. To insure accuracy attempts are made to trap the patient while testing sensation. Care must be exercised to in no way "suggest" any sensory disturbance to the patient.

If anaesthesia is suspected to be hysterical in origin it can be easily proven. The pin point is moved rapidly over the anaesthetic area towards an area of normal sensation, noting carefully where the change in sensibility occurs (it is usually abrupt in hysteria). Later return to the same place only proceed from the normal area towards the anaesthetic skin. The difference in position of the dividing line on the two examinations is often striking. It is often possible to "suggest" sensitive spots in anaesthetic regions to hysterical patients.

In testing pain sensation with pin prick it is important to always employ the same degree of pressure. This comes with practice and in accurately mapping out areas where sensation is only moderated diminished it is absolutely necessary.

Vibration sense—is often difficult to test and impairment is frequently of great significance in diagnosis. It may be tested on all bony prominences on the limbs, hips and spine. As with other forms of sensation one should attempt to trap the patient at frequent intervals to be sure he is answering correctly.

Deep pressure pain is tested by squeezing hard the muscles of the limbs between the fingers and thumb.

Stereognosis should be tested in the hands as a routine. The compass test for two point discrimination need only be used in selected cases.

Sense of position and passive movement — is tested in the upper limbs by having the patient close his eyes and hold his arms outstretched in front. He is told to keep the arms in position and not to allow them to move. If sense of position is defective in one arm it will soon move up or down unknown to the patient while the normal arm remains stationary. The ability of the patient to detect slight movements at the phalangeal joints is tested, normally very small passive movements of the fingers are appreciated.

The lower limbs are examined in a similar fashion. One limb may be placed in a certain position (the patient's eyes are shut) and he is told to imitate the position exactly with the other limb. The big toes are passively flexed and extended, while the patient, with eyes shut, endeavors to indicate the nature of the movement. Normally movements of the toes must be fairly gross to be fully appreciated.

The bones and joints of the skin should be thoroughly examined. The finding of charcot joints, perforating ulcers, herpetic eruptions, neoplasms, etc., are of great aid in diagnosis.

Needless to say all the other systems in the body must be thoroughly examined before a neurological investigation can be considered complete.

I have not mentioned the examination of the cerebro-spinal fluid and several other aids in diagnosis, many of which are of a specialized nature, as they are beyond the scope of this article.

Dementia Praecox.

By J. D. GRIFFIN, B.A., 3T2.

In presenting a summary of modern views on the socalled "Dementia Praecox" form of mental disorder, a brief historical background may be interesting and useful.

Previous to the middle of the last century the attempts at classifying the various kinds of insanity were crude and unsatisfactory. But even at this time there were active groups of men each advocating a different basis of classification . Psychological, physiological, etiological and symptomatological classifications were all advanced—all with some good points in their favour. At this time (1860) a Frenchman, Morel, an exponent of the etiological basis of classification, in a classical paragraph described a number of cases where terminal dementia or complete unrecoverable insanity occurred in young people. This disorder showed various degrees of severity in its onset Morel called this type of derangement "demeno precos."

In 1896 Kraepelin, the German phychiatrist, differentiated between the Manic - depressive psychosis and Dementia praecox; and ever since the term "Dementia praecox" has been more or less generally accepted. This differentiation was based mainly on clinical symptoms and the clinical termination of these cases. The differentiation had considerable prognostic value—because the manic-depressives always got better and the dementia praecox cases always got worse. At about this time Nissel and Algleimer were claiming to show that dementia praecox had a perfectly definite gross and microscopic pathological picture. This led psychiatrists to regard these conditions as being mutually exclusive and to think of them as perfectly separate and definite disease entities.

Then upsetting this clear-cut distinction, cases began to be reported where patients showing the characteristic praecox symptoms got better. One case in particular caused quite an upset. A young man showed typical depressive symptoms of the manic-depressive type, and recovered after a few months. This was all according to Hoyle—but four or five years later, back he came with typical catatonic stupor — one of the forms of dementia praecox. This showed that these conditions were not so mutually exclusive as people had supposed; also, that merely showing the presence of an affective syndrome was not making a diagnosis. These ideas were close to heresy, but they showed that workers were beginning to get a more fluid dynamic concept of mental disorders.

Because the diagnosis of dementia praecox had come to mean a bad prognosis which was not justified and because many cases were seen to have their inception at periods other than adolescence, Bleuler, in 1911, proposed the term ''Schizophrenia'' as a more suitable name for the condition. This literally means a ''splitting of the personality.'' As Adolph Meyer says, as an example, ''an individual meets a problem he cannot react to and this leads to the end result or the 'splitting' with the accumulation of faulty habits of reaction.'' Schizophrenia is the outcome of a progressive maladjustment of the individual to the environment. It is the slow steady deterioration of the entire personality, usually showing itself at the period of adolescence and being made manifest by disorders of emotion, conduct and thought.

Etiology.

There does not appear to be any one single causative agent. Probably the greatest single factor here is heredity with which is intimately bound up psychopathic predisposition. Statistics show that in 50-60% of cases there is evidence of inheritance, the characteristic being a mendelian recessive. There seems to be a tendency ,too, for brothers and sisters to be affected similarly; a so-called ''horizontal'' transmission.

Another factor that has received a great deal of attention is infection, but it is not now believed to be a major factor. Cotton, in Trenton, New Jersey, is the chief proponent of the focal infection theory. Kraepelin believed that an endocrine disturbance was at the bottom of the trouble, and that the condition resulted from an auto-intoxication following a disordered metabolism which in turn was produced by a disordered secretion of the sex gland. By this hypothesis he explained the frequency of the relation between the early symptoms and puberty, disordered menstruation and purbity, disordered menstruation, this idea by the work of Mott (as will be shown) and others working from a pathological angle.

A great deal of recent work has been done by Walker, Hoskins and Sleeper, and others, on metabolism in patients suffering from this condition. These studies tend to show that the basal metabolic rate in Schizophenic patients averages more than 10% below the normal. Many tried to explain these results on the basis of a disordered endocrine system. A recent study by Stevenson and Thomas at the Ontario hospital, Whitby, however shows that there is no constant or definite deviation from the normal metabolism in subjects of this disorder. The metabolic rate appears to vary with the nature of the symptoms, the emotional state o fthe patient and the stage of the disease. And this holds true for most of the physiological studies. They all result in some findings, many of them contradictory. Not many of them explain anything beyond the fact that the whole organism is disturbed.

Precipitating Factors.

Exciting causes may frequently seem to be wanting or inadequate, but a careful study seems to show that mental stress and strain or the so-call psychogenic factors are important. It was Sullivan's (1927) idea that the precipitating cause is the agent which brings to the surface the previously submerged cravings; the resulting psychosis being the attempt by the individual to solve the conflict between these cravings and the standards of adult life. This is made apparent mostly by maladjustments in social relations. Gardner (1930) arranges the precipitating conflicts into three groups which are significant. He claims the greatest number of exciting conflicts are those of a sexual nature, including fear of the result of masturbation. Secondly, we have the conflicts arising from a sense of failure in life plans, such as unsuitable occupations and unfulfilled ambitions. And lastly come those conflicts arising from a long continued feeling of incompetency and inferiority—a general feeling of worthlessness with unsystematized delusions of persecution.

In this connection the work by Pascal and Davasne (1926) is particularly interesting. They argue that the personal "complexes" acquired by the individual are areas of psychic hypersensitivity, which render him liable to break down, when faced with situations stimulating these into activity. In this respect the situation is analagous to an anaphylactic shock—the anaphylaxis or psychosis being stimulated by a variety of agents or shocks such as emotional upsets, or the precipitating conflicts mentioned above. The shock reveals the paths traced by earlier morbid aggressions and discharges itself in directions determined by these. This idea has been utilized to some extent as a basis of treatment. Pascal and Davasne believe that the individual can be "desensitized" by emotional shocks—just as a person sensative to protein can be desensitized by small doses of protein. In the psychotic desensitization the agents used for producing shock are polyvalent and aspecific—i.e., they may be psychic or febrile as in the inoculation of malaria in the treatment of G.P.I. There have been many cases reported where there has been marked improvement following an acute somatic disease or emotional strain.

Toxic and infectious illnesses, however, have been found to play some part as exciting causes. Menninges, in 1926, found that Schizophrenia occurred frequently following influenza, both in normal individuals and in people showing some signs of predisposition by means of careful history taking. Apparently, however, most of the diagnosed cases recovered.

Thus we are confronted with the paradoxical idea that infectious diseases may act as an exciting cause or a cure. One wonders if perhaps the infectious illness may in a great many cases be hardly more than incidental. The main idea seems to be that frequently, when the weakened or predisposed individual is confronted with the stress of puberty, which brings on the sex syndrome, or the strain of adolescence, when he is confronted with problems of maintainence and life work, he turns away from reality, regresses to a more primitive level and becomes psychotic.

General Symptoms.

To describe the general signs and symptoms of Schizophrenia is difficult, for very few cases show identical behaviour. However, a brief picture of the more characteristic symptoms in their usual order of appearance may be useful. Perhaps the most noticeable change is a certain indifference and apathy to the surrounding environment—a listlessness that often passes for laziness. This may be especially noticeable in the individual who previously has been good or even brilliant at his school work. In these cases scolding and punishment do no good and they continue to sit around and stare with apparently no active attention. Gradually a disharmony is observed between the thought processes and the emotional patterns The individual will develop a silly laugh and giggle at the most serious situations. Similarly he will burst into tears when the normal response would be joyful in nature. He shows no insight into these bizarre activities and, as the disease continues, shows increasing general disintegration of the mental functions, with the exception of memory. When there is an opportunity to test this function it appears to be fairly well maintained. Evidently a certain amount of passive attention is given to the surroundings even in the most profound states of stupor. Accompanying this deterioration, hallucination and delusions are often present and these are usually of a peculiar disconnected and utterly fantastic nature. The Schizophrenic individual has his own type of thinking in which he turns inward away from reality, showing the characteristic introversion. In this respect negativism may develop in which he will not only refuse to do anything he is asked to do, but will passively resist any attempt at forcing a particular action, and may even tend to do the opposite. For instance when asked to open the eyes he will very likely close them all the tighter.

The physical symptoms are naurally not constant. A great many cases appear physically normal. Often, however, they appear poorly nourished and below par generally—frequently with a varying amount of vasomotor disturbances and cyanosis. These physical effects may be thought of as wholly secondary to the primary disorder.

In the original conception of dementia praecox it was believed that the age incidence was fairly well limited to below 30 years. Now, although, the great majority of cases (66%) apparently have their beginning before this age, this must not be considered an absolute criterion.

Kraepelin in his original paper proposed several sub-groups, the more important of which are still maintained and used in many hospitals. These briefly are as follows:

1. Dementia Praecox Simplex or Schizophrenia Simplex. This group shows an early gradual devastation of the whole psychic life—leading to extreme apathy and emotional blunting. They exhibit changes in temperament, becoming moody, irritable and asocial. Their thinking becomes disorganized and they are unable to sustain conversation. These people lack ambition, are often shiftless and idle and form a great number of the unemployed class, hoboes and prostitutes, etc.

2. Hebephrenia. Here the same syndrome is present only apparently advanced farther. There is a general incoherence of the train of thought and great emotional disturbance. The emotional response is shallow and generally without adequate cause. There are usually hallucinations, mostly of hearing and occasionally of sight. Ideas of persecution and reference are fairly constant; that is, the individual often fancies people in the street are "referring" to him and talking about him.

3. Catatonia. This form is often very very dramatic in its manifestation. It develops rather suddenly and more acutely than the other types, but in much the same manner. They quickly pass into a state of dull stupor showing extreme mutism. They are usually intensely negativistic, but may show the exact opposite—hypersuggestibility. Often they will show the so-called "waxy flexibility when they allow themselves to be placed in the most awkward positions and keep this position indefinitely. They are apt to be very imitative in speech and action and this may descend to an absolute stereotypy. Sometimes these people may change suddenly from a deep stupor to a period of extreme frenzy when they may become very dangerous.

4. Paranoid states: This form usually develops later in life than the others and is characterized chiefly by the multiple delusions which may be more or less unsystematic and accompanied often by hallucinations. These ideas are either persecutory or grandiose or combinations of these. The termination is similar to the others.

Pathology.

As was pointed out, Kraepelin believed that dementia praecox was due to a disordered secretion of the sex gland. Mott, in England, was able to show definite signs of regressive change in the tests and arrest of spermatogenesis. His co-workers were able to show regressive changes in the ovaries in female patients. Alzheimer was able to show marked sclerotic changes in the nervous system, especially in the 2nd and 3rd cortical layers of the frontal area, and also an increased deposit of lipoid materials and a general hyperlasia of neuroglia. Other workers even went so far as to show different pathological pictures for acute and chronic cases and that different areas were involved for different clinical pictures. Dunlap (1924) carefully checked this work with controls and came to the conclusion that precisely similar changes were found in normal individuals. He stated that many of the findings, too, were due to artefact and defective fixing. Spielmeyer, nevertheless, in a recent article insists that the process of dementia praecox is organic and not functional, arguing that lack of evidence showing pathological change is a negative finding and should not be considered a positive proof of the functional viewpoint. Much work has been done on the changes shown by the various endocrine systems—other than the sex glands—especially thyroid pituitary, and the adrenals,-nor has the biochemical angle been neglected, changes in acid and base equilibrium and blood sugar curves being found in many cases. Kretchmer expresser a very sensible viewpoint when he observes, "we must not lose sight of the brain as the casual factor and think the endocrine is alone responsible—or a biochemical upset either. We must think of it as an intimate biochemical relation between brain and glandular complex."

Diagnosis.

The main difficulty in diagnosis appears in the differentiation from Manic-depressive psychosis. In the depressive reactions of this type of psychosis there is a prolonged subjective feeling of sadness not shown in the Schizophrenia; while in the manic reactions the mood is happy and runs a prolonged course as compared to the more episodic course in Schizophrenia with its characteristic poverty of ideas. In the Manic-depressive reaction there is usually a history of repeated attacks without deterioration. The manic activity in these cases, although changing in character is directed to one purpose, unlike catatonic excitement. However one wonders whether an absolute diagnosis is really important in these cases. There is a tendency nowadays to use the term "Schizoid" reaction rather than the more dogmatic Schizophrenia. This while taking away from the fatalism of the thing which sometimes led to therapeutic nihilism, still determines the treatment.

Treatment.

The treatment is based mainly on working out a satisfactory adjustment to the environment. Occupational therapy appears to be useful in bringing about a suitable social reaction in many cases. The patient's general health must be attended to and all the assistance of peace and quiet and attentive nursing must be used. The taking of histories is very important. The reaction type is carefully considered in all its detail and the personal history is taken fully. This must contain all the important acts of the life history—a sort of longitudinal study of the individual as opposed to a cross-sectional study of his present character. Then this personal history is reconciled with the constitutional picture, and in this way it is determined whether the psychotic reaction is an exacerbation of previous tendencies, or whether it is an entirely new turn of events with new symptoms.

Many patients with Schizophrenic symptoms make excellent recoveries but it is difficult to give a definite prognosis. They form a fairly small percentage of hospital admissions, but a large percentage of the permanent hospital population and we only know the prognois on those schizophrenic states which are of such severity and duration and anti-social effects as to have led to hospitalization. It is believed that large numbers of adolescents pass through phases in which there are symptoms of a schizophrenic type of minor severity. Most of these adjust finally, and apparently only by accident do some go on to the acute phase. It is these acute pernicious forms, then, that are usually studied and discussed and the information obtained may not give us an altogether truthful picture of the prognosis of the disease.

This brings us to perhaps the most important development in modern treatment of psychosis—namely prevention. With the introduction of genetic psychology and schools for child study not only sub-normality is recognized and dealt with, but also abnormality in the shape of early forms of psychoses—especially early schizophrenia. These "nursery-clinics" enable personality studies similar to those devised by Riley to be brought into play and naturally, too, makes possible a much more complete longitudinal personal history. The best example of an early childhood tendency towards Schizophrenia is in children displaying the socalled "shut-in" type of personality. Whereas normal children are more or less manic in activity and thought and show marked extroversion, these children show introversion. This, too, indicates one treatment which is simply a frank understanding of the child's early signs and the introduction of corrective measures which gently but firmly guides the growing mind along the avenue of healthy attitudes, appetites and emotions.

Summary.

The modern ideas on Dementia Praecox, then, can be summed up briefly as follows:

1. Recognition of the concept that the ensemble of conditions which determine living activity cannot be traced to a single isolated cause or factor—or to a number of factors. All the organic and psychic factors which make up our life as a human being constitute a unity—a total state which cannot be dismembered into fragments in an endeavour to say this or that factor causes such a reaction. In short, we must always think of the individual as a whole—an undivided entity. Along with this idea there is a tendency perhaps to pay less attention to dogmatic etiological or pathological concepts of the disease.

2. On the other hand more attention is being paid to the so-called "longitudinal" study of personality with the idea that the more complete the history the earlier the disease will be recognized. In this connection differential studies in childhood promise to be a big factor in determining treatment.

3. Preventive medicine is developing into perhaps the greatest and most useful field of work. With the abolition of unsuitable environmental conditions and the proper guidance through the chaos of adolescence, there is good reason to believe that the incidence of dementia praecox will be considerably reduced and the prognosis greatly improved.

Referances.

1. Henderson & Gillespie—Text Book of Psychiatry.

2. White—Outline of Psychiatry.

3. Strecker & Ebaugh — Practical Clinical Psychiatry.

4. Devine—Recent Advances in Psychiatry.

5. Kraepelin — Dementia Praecox and Paraphrenia.

Pernicious Anaemia.

By F. B. PLEWES, M.A., 3T2.

Historical

The first case of pernicious anaemia to be found in the literature is that described by Dr. Coombe of Edinburgh in 1823, who called it ideopothic anaemia. In 1855 Addison carefully described the clinical manifestations, differentiating it from the disease of the suprarenals which bears his name. It was particularly impressed by the lateness of the loss in weight and the invariably fatal issue. A certain Dr. Leared first described the blood smear. Professor Biernier made the independent discovery of the disease in Germany while apparently ignorant of Addison's work and called it Primary Pernicious Anaemia. Dr. Osler, in 1877, said that Dr. Howard Palmer of McGill had been teaching the disease for years to medical students there. In the early 80's Ehrlich and others described the nucleated red cell forms, macrocytes, colour index and subacute combined degeneration of the cord. The history of treatments used would fill a book, but arsenic, perhaps the most popular, was suggested by Bromwell in 1877. Vital staining was invented in 1907. Splenectomy has been used sporadically since 1913. William Hunter, who studied the disease for many years, was the chief exponent of the gastro-intestinal toxemia concept of etiology. Whipple published his results on experimental anaemias in dogs in 1925, showing the importance of diet in aiding recovery. This led directly to the work of Minot and Murphy and the establishment of the liver diet as specific for the production of permanent remission in pernicious anaemia. Since the publication of their results in 1926, the literature on pernicious anaemia discloses rapid and sure advances so that now we know the peculiarities of this disease as we know few others.

Distribution

There is a much higher incidence of the disease in Ontario than in any other district for which statistics are available. It appears to be found more frequently in Northern Europe, the British Isles and Northern North America than elsewhere.

It is said that while the average practitioner elsewhere sees a case only once in 20 years, in Ontario he will see one every two or three years. In regard to age, it appears to have a higher average at 45 to 55 years.

Notes on Symptoms

Periodic sore tongue is usually the symptom which is first complained of. Tingling and numbness of the extremities is common. Less commonly seen is the lemon-yellow pallor. Obvious pallor does not appear until the red count is very low, when there is often a generalized oedema. Petechial haemorrhages in mucous membranes may be seen, and very often retinal haemorrhages. A patient with congenital achlorhydria should be watched, also those showing unexplained gastro-intestinal trouble, mild fever, dyspnoea atypical spinal symptoms, tabetic symptoms, weakness and general debility. In such cases a blood smear and test-meal may prove illuminating.

The tongue is clean and moist, with soreness around the edges and tip. This is at its worst early in the disease. The papillae may be atrophied so that the surface is smoothed out. The whole organ may become small, and ulceration sometimes occurs.

The pulse is usually well over 80. There may be cardiac pain, even angina, with haemic systolic murmurs and weakness, dyspnoea and palpitation.

The spleen is enlarged in 40 per cent. of cases. The liver may also be enlarged.

The nervous and mental symptoms may occur early in the disease, from a haematological point of view, sometimes even before any blood signs. The severity of these symptoms does not necessarily vary with the state of remission or relapse.

Peripheral neuritis may occur aside from the use of arsenic. The early numbness and tingling of the extremities may ascend the limbs with progressive loss of sensation, sense of position, vibration sense. Motor signs may follow or precede the sensory signs and may be of the spastic or flaccid variety, and an early spastic paraplegia may become flaccid. Loss of bladder and rectal control is a late sign. The superficial reflexes remain active. The nervous signs may be rapid, leading to death in six weeks, or as slow as 12 years or more in onset.

Dimness of vision and flashes of light are common eye symptoms. Ophthalmological examination often discloses oedematous backgrounds with haemorrhages at or near the disc. Usually the urine is of low specific gravity and gives a positive test for urobilin. Fever occurs in two-thirds of the cases, and may be irregular, intermittent, or continuous. It appears to bear no relation to the severity of the anaemia.

Blood System

The blood picture varies according to the stage of relapse or remission. Pernicious anaemia is noteworthy in the fact that no condition presents such oligocythemia without an obvious explanation. It is agreed that it takes at least six months to one year for the count to fall from normal to 1,000,000. It is the slowness of this fall that enables a patient with such a count still to be working.

The Anisocytosis shown in this disease is greater than in any other. The red cells vary from the smallest visible microcyte to macrocytes of 13mu. or more. The diameter of the normal erythrocyte is 7.2 to 7.9 mu. dry, and 6.0 to 8.8 mu. wet. In relapse of pernicious anaemia the red cells may measure say 4 mu. to 3 or 4 times this size, and average about 8.2 mu.

An idea of the size of the reds may be gained in several ways:

(1) By the use of a microscope with a measuring device.

(2) By always using the same magnification in looking at blood smears.

(3) By superimposing a slide with normal blood smear upon the suspected smear, and focussing alternately on the two smears.

(4) By the haliometer, a recent invention making use of the refractile power of the corpuscles to measure the average size of the cells in the smear.

Macrocytosis is the most important finding in the blood smear when pernicious anaemia is a likelihood. (In this connection it should be noted that in thin films the colour is apt to be evenly distributed in the cell, while in thick films central pallor is best seen.)

Megoloblasts are often noted especially when the red count is below 1,000,000, and shows that the bone marrow is under severe functional strain—a greater damage than that shown by normoblasts which may occur in any anaemia. The presence of gigantoblasts gave very poor prognosis before liver was introduced. The Cabot ring and Howell-Jolie bodies in the red cells are remnants of nuclei which have not disappeared, it being generally considered now that the red cell nucleus is not extruded. A blood crisis is said to occur when the smear is flooded with these nucleated forms, especially the megaloblasts. Poikilocytosis is not marked in pernicious anaemia. The variation in the reds is one of size rather than shape. A mild leukopenia is generally found, and this is often proportionate in degree to the severity of the disease. A relatively high lymphoctye count is observed in the differential. If a leukocytosis is present in pernicious anaemia, Davidson and Gulland say it signifies the presence of renal disease in the greater number of cases. A shift to the right—so that there may be 8 or more lobes to the neucleus of the polymorphonuclear cell—is characteristic of megoloblastic anaemia. This is also noted in hepatic and Hodgkin's disease, and is contrasted with the shift to the left in septic conditions. Giant polymorphonuclears may appear in severe relapse.

The platelets are invariably very low in number, though larger in size.

The colour index is a most important point in diagnosis. But it is valueless if the haemoglobin estimation is not accurate. In the best natural remission the colour index may be as low as 0.8, but it is nearly always below this in secondary anaemias. In relapse, with low red counts, it may reach 1.5.

An increase in the number of reticulocytes marks a remission either natural or after liver. The reticulocyte count may be done as follows: After vital staining of a smear count 500 or more red cells, noting the number which are reticulated. Polychromasia and reticulation are supposed to be the same thing. Reticulocytes are larger and stickier than the normal red. Their temporary increase after treatment is of greatest prognostic importance. The reticulocyte response will be considered further under treatment.

Pathology

The post-mortem findings are distinguished by: little loss of fat; the grapefruit tint; fatty degeneration of the kidneys, gastro-intestinal walls, liver, heart, vessel walls and other organs; iron deposits in the spleen and liver, both of which may be enlarged. The bone marrow appears like the haemoplastic tissue of childhood, the normally white marrow being red and congested, with absorption of bone trabeculae. Yellow wavy lines are found in the left ventricle. The blood is watery and the brain of a greenish tinge, with microscopic examination revealing degeneration corresponding with the neurological symptoms.

Aetiology

The theories which have been advanced are too numerous to discuss. Hunter suggested a streptococcus, which he isolated from the tongue. An abnormal metabolism of the reticulo-endothelial system has been another suggestion. The achlorhydria has usually been considered of significance, and some have pointed out that the intestinal flora is abnormal right up to the duodenum in pernicious anaemia. The theories of autointoxication and infection have been especially prominent. A recent article by Castle, Townsend and Heath marks a real contribution to the subject of etiology. By repeated experiments, in which they fed pernicious anaemia patients many different diets, they found that there was required to form an effective substance, such as is present in liver, an intrinsic factor present in normal gastric juice and an extrinsic factor present in beef juice. The achylia gastrica of the affected person results, according to them, in a deficiency in diet by defective digestion of protein. (Many people do not secrete HCl and yet have not pernicious anaemia. Such have a secretion from their gastric mucosa which persons with pernicious anaemia have not. Recent work has resulted in a new conception, the pernicious anaemia family, which consists of people who show secondary anaemia and abnormal bone marrow and who are more likely to develop the clinical disease than persons with normal gastric juice.)

As in diabetes the pancreatic function and carbohydrate metabolism, so in pernicious anaemia gastric function and the manipulation of proteins are altered; in each, the dysfunction of islets and of gastric mucosa is unknown. The specific factor is like an enzyme protein in type, destroyed at 70 to 80 degs., absent in saliva and duodenal juice, and active in neutral solution. Thus this disease can be added to the list of deficiency diseases, since the lack of the intrinsic factor is the essential defect leading to development of pernicious anaemia. They add that tests for the presence of HCl and pepsin in gastric juice are not of conclusive value in determining the absence or presense of the intrinsic factor.

Diagnosis

The diagnosis need not depend on all the symptoms outlined above. Indeed cases must be diagnosed without any gastro-intestinal disturbances, or without the typical blood smear, or without the neurological signs of numbness and tingling, with loss of vibration sense. Undoubtedly the first suspicion is aroused by the examination of the smear, or the sore tongue, or achlorhydria, or urobilin in the urine, more often than by the lemon pallor. It is not surprising to find it difficult to say whether or not a smear is that of pernicious anaemia, in view of the many disturbances of the blood picture that may occur. The colour index is a very conclusive test if done carefully.

The reticuloycte response to treatment with liver is diagnostic. Recticulocytes are young red cells, fresh from the marrow, and present normally as 0.1 to 1% of red cells. They are detected by vital staining as before described. The patient who is suspected of pernicious anaemia is put on a diet high in liver or liver extract of proven potency, in amounts larger if anything than the prescribed dosage. The recticulocyte count is then done at least once daily until it is back to normal, or for ten days. It will be found that there is a sharp rise in the percentage of recticulocytes, if the initial red count is under 3,500,000; above this no such response can be expected. The response is in proportion to the oligocythemia and the amount of liver; it begins on the 2nd to 5th day and is at its maximum on the 5th to 8th day and is back to normal on the 10th to 20th day. It is very useful to draw a graph to express the rise in relation to the days after beginning of treatment as it is usual to express results in this manner in the literature. The potency of liver extract has always to be tested on patients so that it is not as reliable as some other drugs. A low, long curve indicates insufficient liver or infection. The maximum responses found was 87.7% at initial count of 1,000,000 reds, 8.4% at 2,500,000, and 0.3% at 3,600,000.

Differential Diagnosis.

The following conditions may be confusing: Carcinoma of the stomach (retinal haemorrhages, low counts, age, smear, colour index), chlorosis (smear), septic anaemia (polymorphonuclear leukocytosis), chronic haemorrhagic anaemia (occult blood and colour index), sprue (tropics, emaciation, stools), leukemia with overradiation (allow white count to remain over 20,000, low colour index at first), aplastic anaemia (chronic from X-ray or radium, no regenerative signs, no liver response), acute lymphadenoma (rare, large glands, high percentage reticulocytes). The bracketed words suggest the points on which a differential diagnosis may rest in the event of the preceding condition being suspected. Murphy and Fitzhugh have recently suggested that the blood cell volume is helpful in differentiating pernicious anaemia from anaemia conditions of the secondary type, except aleukemic leukemia, which is, however, very rare. They also add that with liver the volume index returns to normal. Vol. index is expressed as percentage of normal cell volume (percentage of normal red count), and is found to be over one in pernicious anaemia. The normal cell volume is 4.8 c.c. in 10 c.c. of whole blood. The polychromasia, megalablasts and megolocytes seen in the smear are valuable confirmatory evidence of pernicious anaemia, showing as they do an overworked bone marrow.

Course.

The onset of the disease is slow and insidious. Recent workers have gone so far as to identify a pre-pernicious anaemia condition, predicting the appearance of the disease and advising prophylactic treatment. As pointed out above, the typical case with textbook symptoms all present is apt to be a rarity and one group of symptoms is liable to obscure the rest. The patient may go on about his business till late in the disease, when dyspnoea and weakness from a red count of 1,000,000 brings him to the doctor, or spastic paralysis doubles him up so that he cannot walk. Gastric disorders and voracious appetite are early signs, while nausea, drowsiness, delirium, and paraesthesis are usually late. The subacute combined degeneration of the cord may be demonstrated by increased or absent knee jerks, clonus, Babinski, and ataxia, with similar phenomena such as Rhombergism and loss of sensation to a tuning fork or bony prominences. Loss of weight is a very late sign and an increase in the early stages is rather to be expected. Death is usually cardiac, but may result from the lowered resistance to infection. On the other hand a remission up to ten years' duration may occur without liver, and remissions up to 2 or 3 in number are a common feature.

Treatment.

The probable importance of diet has been mentioned by Habershon as early as 1861 and by Osler, but beyond generalities regarding high protein, iron and high calories, no specific suggestions of value were forthcoming till 1926. Whipple, from his work on experimental anaemia in dogs, was the first to suggest that liver might supply the material going to the formation of red cells which appeared to be lacking in pernicious anaemia. It was pointed out that absence of the disease occurred in certain districts where the diet contained less of dairy products and free sugar and lipoids, with increased muscle meat. Gibson and Howard suggested liver treatment as a result of Whipple's work, to be combined with iron-rich foods.

But it remained for Minot and Murphy to point the road which led to the successful treatment of pernicious anaemia. They published the results of treating a representative series of 45 consecutive cases with a diet rich in protein, iron, and especially liver, together with 15 c.c. dil. HCl daily. Every one of their cases who maintained the diet showed improvement. Their article in the American Medical Association Journal of August 14th, 1926, is well worth reading, showing as it does the well-planned, well-executed research and conservative conclusions which so often marks the achievement of another distinctly forward step in the march of science. Their cases included patients in practically all stages of the disease, and their claims for the treatment appear decidedly not extravagant from their results. They state a fact that was too often ignored in former papers claiming to set forth cures, that no single case of their 45 was such that the remission could not be paralleled by a natural remission. They showed that an inadequate liver diet resulted in slow improvement and relapse. That splenectomy causes remission in 64% of cases, transfusion in 50% cases, high caloric diet in 65% of cases, made it necessary that the figure of 100% remission from this treatment be obtained in order that claims of permanent remission could be made. They conclude with the admission that these 45 cases may be unusual or accidental, but say that they believe the liver diet to be wise treatment, as did Gibson and Howard.

Since the appearance of Minot and Murphy's article the whole subject of aetiology, diagnosis and treatment of pernicious anaemia has progressed by leaps and bounds. As recently as three years ago the diagnosis of pernicious anaemia outside of the Peter Brent Brigham Hospital in Boston where these experiments were still being carried out, meant speedy death—a prognosis with far less hope than in coronary thrombosis. Now there is probably no disease, with such rapid and complete recovery. The treatment is far simpler than that of diabetes, as those who have tried to figure out a diabetic diet will testify. Though large quantities of liver are advised at first, say 300 gm. daily this quantity may be reduced to 150 gm. daily if found to be sufficient after the blood picture is normal, in cases uncomplicated by combined degeneration of the cord. Liver extract is just as good as whole liver, if properly made, and may do away with any hardship the patient may suffer from the constant eating of liver in its more obvious forms.

It has been stated rather generally in the literature that subacute combined degeneration of the cord in pernicious anaemia prevented a total recovery by a liver treatment. Some claimed that the nervous lesions progressed under even large doses of liver. Since degeneration of the posterior and lateral columns appears to be a complication present in a large proportion of cases, this belief was a distinct fly in the ointment when a prognosis was made with such signs present.

A paper by Farquharson and Graham appearing recently shows that more optimistic views may be taken. From observation of 50 patients, they state that early cord symptoms such as paraesthesia, for a few months disappeared with adequate whole liver therapy. In more marked cases the improvement was slow and most marked between the 2nd and 12th months. Of 18 cases showing marked cord changes, 10 became better, 4 improved but were still unable to work, in 2 the process was arrested, and 2 died from other causes. It is to be noted that in no case did the lesion progress as had been previously reported. Of 4 cases showing mental symptoms of ugliness of temper and irritability, 1 died of pneumonia, 1 recovered and 2 improved. A few of those cases which did not persist in the liver therapy, developed cord symptoms, and 3 of these had haemoglobins of 70 and were feeling well, while the others had an anaemic relapse as well as the cord symptoms. The authors stress the importance of an adequate amount of liver, and favor whole liver, rather than extract. Untested liver extract should not be used except under careful observation. Inadequate therapy may maintain red counts of 4,000,000 but not stop the progression of nervous symptoms, so that 250 gm. of liver or the broth from 1.000 gm. is advised with the dose made up next day if liver is omitted at any time. After six monthe the dose may be reduced to 150 gm. Regular examination of the patient appears to be wise, as many patients have been found going around with a haemoglobin of 60 or 70% at which figure there is danger of serious nervous lesions being manifested.

Another recent article by Wilkinson & Brockbank advise the retention of HC1 therapy, and the use of pepsin for flatulent dyspepsia, diarrhoea, and urticaria found sometimes in patients on liver treatment. Their routine prescription is 3 parts of glycerinum pepsini in 1 part dilute HC1 of which 2 drachms is to be taken in 8 oz. of flavoured water and sipped throughout the meal.

As substitutes for pork or beef liver there have been several suggestions. Connery got good results with fish liver extract, from such fish as cod and haddock, in 60 gm. daily doses. Sturgis and Isaacs found that whole chopped hog stomach, dessicated and defatted, in doses of 20 gm. or so, induces remission and maintains it at 7 to 10 gm. daily using 10 gm. per 1,000,000 red cells deficiency till the count is normal. They found that the active substance was contained in the mucosa and corroborate Castle's theory of aetiology. They report an average increase of 500,000 reds per week for eight weeks. This preparation is odourless and tasteless and is used as a puree in tomato juice. The use of kidney is often referred to, but insufficient work has yet been done for the evidence to be anything more than suggestive.

So at this stage, we have a definite treatment and a bright prognosis to offer the patient who is diagnosed as suffering from pernicious anaemia. The prescription for the patient would probably run as follows: a balanced diet containing milk, green vegetables, fresh fruit, red meat and 150 or more gms. of liver or its equivalent in extract, and a mixture of HC1 and pepsin to be sipped during the meal. A larger dose of liver is used until remission is assured and the blood picture normal. Under such treatment, the patient loses his fever and soreness of the tongue in a few days. The bilirubinemia and the deficiency in his haemoglobin and red cell count, is completely restored in 3 months. Probably at the end of this period the patient exuberantly states that he has not felt as well for 6 months to 10 years or more. The patient without nervous complications is kept in bed till his haemoglobin is well over 60, with nervous manifestations relieved or stationary for months. If such a recovery does not take place infection should be looked for, and Professor Graham in one of his articles states that the respiratory tract and prostrate are the most frequent sites. If the patient is too ill to take adequate liver, a transfusion may be necessary to start a remission, but after a week or so on small amounts, the patient usually becomes ravenous.

An advantage of such therapy is that the diagnosis is clinched by the treatment. A reticulocyte count should be done daily in all cases of pernicious anaemia for the first two weeks or so after treatment is begun, both to follow the effect of the liver on the patient as to adequacy and presence of infection, and from a scientific interest, for this subject is not yet exhausted by any means.

Liver has been found useful also in sprue, in anaemia accompanying pregnancy, in secondary anaemia resulting from gastric haemorrhage, and in nutritional anaemias, but not in aplastic anaemia. The failures reported in the treatment of pernicious anaemia are due to an inadequate liver therapy by the use of untested liver extract or the patient's carelessness in daily dosage. For this reason a Hb estimation should be done every month and the Hb maintained over 90.

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The Pathology of the Pancreas in Diabetes Mellitus.

By E. H. BENSLEY, B.A., 3T0.

Historical Review

The pursuit of many investigations into the chemical physiology of diabetes mellitus with the establishment of routine methods of determining quantitatively blood and urinary sugar, the development of a suitable dietetic treatment of this disease, and finally the isolation of insulin have engendered enthusiasm for the biochemical aspects of diabetes mellitus and distracted attention from its pathology. The study of pathological changes in the pancreas, in the past, has contributed much to knowledge of this disease. First, the finding of a diseased pancreas in a certain number of cases of diabetes helped to draw attention to the pancreas as the site of the causative lesion. Second, at a later date, the finding of cases of diabetes in which only the islands of Langerhans and not the acinar tissue was diseased lent considerable support to the insular theory of the origin of diabetes. Third, the study of the pathology of the pancreas in diabetes has led us nearer to a knowledge of the aetiology of this disease than any other method of approach. Fourth and finally, an understanding of the pancreatic changes in diabetes, particularly hydropic degeneration, by making clear that failure to relieve diabetic signs and symptoms results in further pancreatic destruction, has emphasized the importance of dietetic and insulin therapy and elevated it above the level of purely symptomatic treatment. These are the main contributions of investigations into pancreatic pathology to knowledge of diabetes. In spite of what has been accomplished, the lesions of the pancreas in diabetes are still very imperfectly understood.

In 1911 Weichselbaum reported 183 diabetic necropsies, on the basis of which he stated that the three principal lesions causing diabetes were hydropic degeneration, fibrosis and hyaline degeneration affecting the islets. In 1913 Allen brought forward evidence that hydropic degeneration is not a cause, but a result, of diabetes, being due to functional overstrain of the island cells. In addition to making this important contribution, Allen has reviewed the whole subject of the pathology of diabetes as well as pursuing a large number of original investigations on various aspects of the subject. On the basis of this work he has introduced several broad conceptions regarding the pathology of diabetes, of which the following are the most important. First, diabetes probably cannot exist without pancreatic disease. Second, in the majority of cases the important lesion is a pancreatitis. Third, few escape some pancreatic injury, a normal pancreas at autopsy being perhaps the exception rather than the rule.

The Normal Pancreas

The pancreas lies retroperitoneally in the upper part of the abdominal cavity in relation with the posterior abdominal wall. It is divisible into three portions—the head, body and tail. The head, which forms the right extremity, is broad and lodged within the curve of the duodenum. The body, somewhat prismatic in shape and narrower than the head extends across the mid-line to become continuous with the narrow left extremity or tail of the pancreas which lies in contact with the spleen. The organ is soft in consistency and presents a surface which is slightly irregular due to a network of sulci, representing the boundaries of the lobules of the gland. Normally this lobulation is rather obscure. The pancreas possesses two ducts as a rule. One, the main duct or duct of Wirsung, runs from left to right through the pancreatic substance, receiving, in its course, the ducts of the various lobules. It unites with the common bile duct to form the ampulla of Vater in the wall of the duodenum. The ampulla, in turn, opens into the duodenum on the duodenal papilla. The second duct, the accessory duct or duct of Santorini, arises from the main pancreatic duct in the head of the pancreas and opens into the duodenum separately above the duodenal papilla. This accessory duct is sometimes obliterated in the course of development.

On microscopical examination of a section of the pancreas, one finds the parenchymatous tissue to be divided, somewhat imperfectly, into lobules by bands of fibrous tissue. This fibrous tissue is termed interlobular. This is continuous with the fibrous tissue, scanty in amount, which extends into the lobules. This is termed the intralobular or, since it lies between individual glandular acini, interacinar fibrous tissue. Within the fibrous tissue are ducts which ultimately fuse to form the larger ducts described above. The parenchymatous tissue consists of two distinct elements—the glandular acini and the islands of Langerhans. A detailed description of the acini is unnecessary for the purpose of this thesis. The islands of Langerhans are responsible for the production of insulin and disease of these structures causes diabetes. Therefore their structure will be described in some detail. These islands are not uniformly distributed throughout the pancreas, being more numerous in the tail than in the body or head of the gland. An island is round or oval in shape with a regular outline. The diameter varies from 100 to 400 microns, islands exceeding 400 microns in diameter being very rare in the normal pancreas. It is composed of epithelial cells, more or less polygonal in form and each possessing a large round nucleus and finely granular cytoplasm. These cells form a network of irregular columns. In the meshes are numerous capillaries carrying with them a very small amount of delicate connective tissue—the intra-insular fibrous tissue. The great vascularity of these islands is a very marked feature. They are much more richly supplied with blood than the glandular acini. By the use of special staining methods it is possible to distinguish at least two types of epithelial cells in the island,—the alpha and beta cells. The alpha cells are larger and much fewer in number than the beta cells and their cytoplasmic granules stain differently from those of the beta cells. The beta cells, composing by far the greater part of the island, are much smaller and are closely packed in rows along the blood capillaries. It is thought that it is the beta cell which is concerned in the production of insulin. A third type of cell — the gamma cell—has been described but little is known regarding it.

In its embryonic development, the pancreas arises as two separate outgrowths, one from the dorsal surface of the duodenum a little above the common bile duct, and one from the lower part of the common bile duct. The former gives rise to the "dorsal" pancreas, the latter to the "ventral" pancreas. These fuse so intimately that no separation line can be distinguished. The duct of the dorsal pancreas is the duct of Santorini and that of the ventral pancreas the duct of Wirsung.

(1) Inflammatory Changes With Fibrosis.

(*a*) *Interacinar Pancreatitis.*

This form of pancreatitis is so named because, in it, there is marked increase in the intralobular or interacinar fibrous tissue with but little change in the interlobular tissue. In contrast with other types of pancreatitis, the islands of Langerhans are involved by the fibrosis more markedly than are other parts of pancreatic tissue. In the early stages of fibrosis of the islets the latter are surrounded by capsules of fibrous tissue which are thicker than the normal almost invisible sheaths and the fibrous coating of the intra-insular capillaries is increased in thickness. At this stage the cells of the islet may show little change in appearance. In the more advanced stages the islets are embedded in dense fibrous tissue which separates them widely from the surrounding acini and the intrainsular sclerosis is very marked. The islet cells are reduced in number, are small and compressed or may be entirely absent, the islet being represented merely by a mass of fibrous tissue. The acini first to be destroyed are those in the neghborhood of an islet. Thus it would appear that the fibrous tissue commences in the islet and then later spreads out into the interacinar tissue. Fibrosis is the main evidence of inflammation when the tissue is seen at autopsy and represents one or more past attacks of pancreatitis or a chronic pancreatitis.

Fibrosis of islets, usually with interacinar scelerosis, is the commonest lesion found in cases of diabetes.

The aetiology of this lesion is not understood. The fact that the inflammatory changes appear first in the most highly vascularized part of the pancreas—the islets—and then spreads from them, suggests that this type of pancreatitis is due to toxins or infectious organisms reaching the pancreas by the blood stream. The lesion is often associated with arterio-sclerosis of the pancreatic vessels.

(*b*) *Other Types of Pancreatitis.*

It has been pointed out that interacinar pancreatitis probably commences in the islets and that the islets suffer most from the inflammation with the consequence that diabetes often results. In other types of pancreatitis, however, the opposite holds true, namely, that the islets are the last element in the pancreas to be affected. They are involved only when the pancreatitis is very far advanced and therefore diabetes results infrequently.

(i) Interlobular Pancreatitis.

In this type of pancreatitis the interlobular fibrous tissue is much increased while the interior of the lobules, including the islets, are free from fibrosis as a rule. Invasion of the lobules commences at the periphery. In most cases the islets of Langerhans are completely unaltered even with great destruction of acini. One may find healthy islets completely isolated in stroma, the acini in the neighbourhood having been destroyed. It is only when the sclerosis is very far advanced that the islets begin to disappear due to interference with blood supply and compression of their cells by the contraction of surrounding fibrous tissue. Thus diabetes does not develop commonly with such a lesion and then only very late.

Interlobular pancreatitis is due to ascending infection of the pancreatic ducts. It is often associated with obstruction of the duct, the obstruction favoring ascending infection and probably also producing inflammation in itself as a result of retention of secretion. The case described by Cawley was of this type, obstruction being due to pancreatic calculi.

(ii) Syphilitic Pancreatitis.

The type of lesion which is most commonly produced by syphilitic involvement of the pancreas and the frequency with which syphilitic pancreatitis causes diabetes are matters in dispute.

Syphilitic pancreatitis may be either congenital or acquired. According to Opie (3) congenital syphilitic pancreatitis results in proliferation of interlobular and interacinar tissue with destruction of acini, but little or no involvement of islets. In acquired syphilitic pancreatitis one finds irregular scar-like bands of fibrous tissue penetrating the parenchyma. In these bands gummata may be found. As in the congenital form there is little tendency to insular involvement. Occasionally one meets with advanced cases of syphilitic pancreatitis in which practically the whole pancreas is transformed into a fibrous or fibro-gummatous mass. In such cases the islets may be involved and diabetes result, but this is rare. Most investigators, including Allen (2) agree with this description by Opie believing that syphilitic pancreatitis does not tend to involve islets and is a rare cause of diabetes. However, Warthin states that, although lesions similar to those described above with little insular involvement may occur, the commonest lesion resulting from syphilis is an interacinar pancreatitis. Certainly syphilis may give rise to lesions of the pancreas differing markedly from interacinar pancreatitis and not showing tendency to insular involvement, but whether these or interacinar pancreatitis are the more common lesions in syphilis cannot be stated at the present time.

(2) Degenerative Changes in the Islets.

(*a*) *Hyaline Degeneration.*

This lesion shows a striking tendency to select and destroy the islets and, in most cases, leaves the secreting parenchyma almost unaffected.

The first change appears to be a slight enlargement of the islet cell, the cytoplasm of which takes on a staining quality similar to that of hyaline material with special hyaline stains. Later the cell nucleus disappears and the protoplasm becomes homogeneous. The cell is transformed into an irregularly polygonal mass of hyaline material which has a marked affinity for acid stains, staining bright red with eosin. These masses of hyaline material thus formed tend to fuse together and form larger rounded masses. As the process advances, one finds that the cells of the islet have been replaced almost entirely by hyaline material and between the hyaline masses is seen only the occasional compressed cell. In a further stage, the hyaline substance occupies almost the entire area of the island which is thus represented by a circumscribed hyaline structure composed of broken twisted columns of hyaline material between which are the capillaries. The nuclei of the capillary endothelium persist after destruction of the epithelial cells but finally disappear while the capillary lumen remains patent. Hyaline degeneration of the islets may occur without any other pancreatic change, but it is usually associated wth intrainsular and interacinar fibrosis.

This lesion occurs next in frequency to fibrosis of the islets as a diabetogenetic lesion.

(*b*) *Amyloid Degeneration.*

With general amyloid disease, microscopic examination of the pancreas usually demonstrates the presence of amyloid there. Deposits of amyloid are found in the walls of the interlobular arteries, of interacinar capillaries and of the capillaries of the islets of Langerhans. It is of no practical importance as a diabetogenetic lesion.

(3) Necroses.

(*a*) *Focal.*

(i) Confined to Islets—'Weichselbaum's Atrophy."

A form of necrosis, focal in that it is confined to the islets, the acini being unaffected, was described by Weichselbaum and Stangl in 1901. They spoke of it as "atrophy" of the islets. Since that time it has been referred to in the literature as "Weichselbaum's atrophy." The affected islet cells are shrunken with pycnotic nuclei and scanty cytoplasm. In the early stages, when the nuclei begin to show the pycnotic change, round celled infiltration, sometimes with slight fibrosis, may be seen in the islet. Later fibrosis of the islet becomes more marked. Allen (5) states that this "atrophy" is probably never found without some degree of fibrosis of the islet.

(ii) Not Confined to Islets.

In this type of focal necrosis, necrotic foci are found scattered through the pancreas affecting both islets and grandular acini. The foci involve small areas containing a number of acini and within some of these areas a necrotic islet may be included. In the necrotic area there is slight proliferation of interstitial tissue.

This lesion is commonly found in the poncreas, but rarely is severe enough to produce diabetes.

(*b*) *Diffuse—Acute Hemorrhagic Necrosis.*

This lesion will not be considered in any detail because to do so would almost constitute a thesis in itself, and it does not play an important part in the causation of diabetes. Acute hemorrhagic necrosis of the pancreas is a disease entity of unknown aetiology characterized by relatively sudden extravasation of blood into the pancreas with widespread necrosis of pancreatic tissue. This is followed by an inflammatory reaction. Very commonly death occurs in a short time, but if the patient survives, extensive fibrosis follows and occasionally diabetes develops.

(4) Pigmentation-Hemochromatosis.

Hemochromatosis is a disease entity characterized by the presence throughout the body, particularly in the liver and pancreas, of deposits of an iron containing pigment—hemosiderin—and the association of cirrhosis of the liver wih this pigmentation.

In the pancreas are found deposits of yellow iron containing pigment in the epithelial cells of both acini and islets. When pigment is moderate in quantity, it occurs as relatively fine, round granules in the cytoplasm of the cells. Wih greater accumulation almost the entire cytoplasm is occupied by them. At the same time the nucleus becomes smaller, irregular assumes a shrivelled appearance and finally disappears, the cell being represented by a mass of pigment retaining the cell outline. Finally the shape of the cell is lost and the clump of pigment particles lies free in the tissue. In this way destruction of both islet and acinar cells occurs. Associated with this is marked interacinar and intrainsular fibrosis. This is probably due to irritation produced by the products of epithelial cell degeneration and the pigment lying free in the interstitial tissue.

Not infrequently the destruction of islet cells is so great that diabetes results. This is often associated with bronzing of the skin due to deposition of pigment there and the name "bronze diabetes" has been given to this syndrome. Hemochromatosis is a rare disease and only a few cases of diabetes are due to it.

(5) Congenital Developmental Deficiency of Islet Tissue.

By this is meant a deficiency of islet tissue resulting from failure of formation of the normal amount of islet tissue in the course of embryonic development.

The possibility that congenital developmental deficiency of islet might be a cause of diabetes has been much discussed and it has been thought that such a condition might account for cases of diabetes arising at an early age and also for some cases of apparently hereditary diabetes. Two cases of undoubted congenital developmental deficiency of islet tissue have been reported. Such cases of undoubted congenital developmental pancreatic deficiency are extremely rare. It must be admitted, however, that it is still possible that minor degrees of congenital deficiency, which would be difficult to detect, may occur and predispose to diabetes by making it possible for diabetes to be produced by an amount of injury less than that which would be required if the congenital defect were not present.

(6) Functional Deficiency of Islet Tissue.

It has been observed repeatedly that, in some cases of diabetes, examination of the pancreas, although revealing pathological change, shows the presence of normal appearing islets in such large numbers that diabetes would not be expected to occur. Also the grade of severity of the diabetes does not always correspond to the amount of normal appearing islet tissue. It was thought that possibly these islets which appear to be normal with ordinary stains might consist only of the alpha cells, all the beta cells, which are considered to produce the insulin, having been destroyed. Sometimes such islets, made up only of alpha cells, are seen in experimental animals. Accordingly Martin (4) applied special granule staining methods for the differentiation of alpha and beta cells to these cases in which the amount of islet tissue did not correspond with the clinical findings. However. with these special stains the islet tissue appeared perfectly normal, large numbers of beta cells being present. Therefore one must assume that islet cells, although appearing normal, may not be functionally normal.

(To be Continued.)

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Lead Poisoning.

By I. W. DAVIDSON, 3T4.

Introduction.

Lead poisoning is not only the most common poisoning in industry, but we find it also derived from such diverse non-industrial source as water supplies, cosmetics and drugs, and home-made beverages. Lead poisoning is a preventable disease and is in evidence in various pathological forms. There are such well-known effects as the stippling of blood cells and secondary anaemia. Its effect on the grem cell produces premature delivery and still-birth; the well-known lead line of the gums, lead colic, lead palsy, and various acute mental changes. But within the last ten years with studies of public health and industrial hygienic conditions, with the requirement of prophylactic measures and our modern knowledge of lead, the incidence of industrial lead intoxication has been greatly reduced. With proper precautions it should be possible to control lead poisoning completely, and thus avoid the need of eliminating the use of lead in industry.

Effect on Blood Corpuscles.

It is our purpose in this article to include only a discussion of the various toxic manifestations of plumbism in the light of the data bearing on the physiology of their production. In the first place, let us consider the effects of lead on the blood cells—for changes in the blood are often the first and most important sign of lead poisoning in man. These effects of lead are (1) stippling of the blood cells, and (2) secondary anaemia.

(1) Stippling of red blood corpuscles has long been recognized. This condition has been described as the presence of basophilic granules in certain red cells. This, however, is not a specific sign of lead poisoning. But the occurrence of stippling in the red cells in various other conditions is relatively rare and slight as compared with the frequency and intensity of its appearance during plumbism. For this reason the demonstration of stippled red cells in blood has come to be considered an almost definite evidence of absorption of lead.

These basophilic granules are formed by some degenerative process from the basophilic substance of young corpuscles which normally gives them their polychromatophilic appearance. Lead has never been known to produce stippling "in vitro" and it is rather interesting to note that there is an apparent restriction of stippling to certain species. In man, rabbit, guinea pig, and rats, plumbism is characterized by appearances of these basophilic granules in red blood cells, but in blood of cats, chickens, pigeons and amphibia, stippling has never been produced, in spite of the fact that corpuscles of amphibia and birds are known to contain basophilic substances. It is true that occasionally a suggestive mottling appears, but certainly no definite stippling. This probably implies a biological and perhaps chemical variation between red blood cells of different species.

(2) The other important blood change caused by lead is anaemia—described as a pallor of tissues and and thinness of blood. It has been found that in lead poisoning the number of red blood cells is much lower than normal, and in fact, in experimental work in some animals anemia is considered an index of degree of lead poisoning. Anaemia then has been attributed

both to peripheral destruction of blood and to lesions in the bone marrow resulting in insufficient production of blood cells. Since lead seems to affect directly the corpuscles in circulating blood, it is of prime importance to understand the physical nature of the reaction, and many "in vitro" and "in vivo" experiments were performed to afford an explanation of anemia of lead poisoning These would take far too much space for a detailed discussion and Aub has presented a very complete and satisfactory summary of action of lead on the blood.

"In vitro" exposure to a very small amount of lead greatly alters the surface of the red blood cells and causes them to shrink and their consequent relative impermeability to water renders them incapable of swelling as much as normal cells. This enables such cells to withstand a marked increase in their resistance to different osmotic surroundings, evidence for which is found in the abnormally small degree of hemolysis in salt solutions of very low concentration. This suggests that "leaded" cells should be really stronger than normal cells, but this is not the case. On the contrary, "leaded" cells are relatively short-lived and haemolyse readily. Experiments performed on rabbits, suffering from acute lead poisoning, show that these phenomena also occur "in vivo." In addition to causing these changes in permeability, lead also alters the physical properties of red blood cells, so that they lose their normal stickiness, and are no longer agglutinated. All these changes are evidence of surface alteration in the cell. The interior of the cells apparently is not affected, for experiments have shown that the physiological properties of the hemoglobins remain normal.

Explanation.

Now we come to the explanation of these changes, and apparently they all depend on the union of lead with inorganic phosphate and are largely surface phenomena. It has been shown that when lead chloride interacts with inorganic phosphate, free acid is liberated. This might be of importance in explaining the action of lead salts on red blood cells. Although buffer action would prevent any appreciable change in hydrogen ion concentration of blood as a whole—there might be a marked local temporary change at surface of cells. Here the objection may be raised that normally the buffers of the blood are quite adequate to take care of any acid produced but we must remember that we are dealing here with a cell surface capable of local reactions and variations in permeability and furthermore one of the principal buffers, the phosphate, interacts with lead to form insoluble phosphate and free acid. so that its buffer action is diminished. These reactions cause the "leaded" red blood cells to change from an elastic, distensable sac to one which is contracted, relatively inelastic, and brittle. In such a condition the cell can so poorly withstand the trauma involved in circulation that this lack of resistance probably explains the marked destruction of peripheral blood in lead poisoning. Because of the loss of circulating red cells in this way, there is a compensatory regeneration of erythrocytes. Many of these young cells are affected by lead after they enter the circulation, so that their basophilic substance is coagulated or clumped together, and they give the characteristic granular appearance—stippling.

Effect on Germ Cells.

The effect of lead on the red blood cells may well be merely a striking example of an action which takes place in other cells of the body. Experiments indicate that germ cells are affected, but data are generalized and only indicate that when either parent is subjected to action of lead, development of young, impaired. It has been clearly demonstrated that lead does not kill the germ cells, but only harms them so that the foetus dies or is undersized. Injury is possibly caused in part by a reaction similar to that occurring in red blood cells and in muscles, but it has been suggested that it may also result from a special susceptibility of fetal tissues to toxic action of lead.

Lead Line of Gums.

The most constant sign of plumbism and one which appears in no other condition except possibly bismuch poisoning, is so-called Burtonian or lead line in the gums. which occurs typically in the gingiva near the border of the teeth and is seen near decaying teeth, either in gums or in mucosa of lip of cheek opposite these. Moreover, rapid caries seems to develop whenever a lead line appears near teeth apparently in good condition. That the pigmentation is not on the teeth themselves, may be easily demonstrated by inserting paper between teeth and gums and also since the true lead line can never be rubbed off, it must be within the tissues and not be merely a surface deposit of pigment. Microscopic examination shows that line is composed of black, irregular amorphous granules, entirely subepithelial. These occur in the interior and walls of blood vessels, in fixed cells of the connective tissue and especially in papillae, which run to base of epithelium. To explain the formation of the sign which is so indicative of lead absorption, several theories have been advanced. All assume the coloration in tissue is caused by interaction of dissolved lead and water which forms black lead sulphide. There are two sources of gas in the mouth: (1) debris of protein food caught between teeth, and (2) decaying gums and teeth themselves. This explains the rarety of leadline formation if teeth are cleaned regularly. In all probability, lead as the tertiary phosphate in colloidal sol. is carried to the gums, just as it is to other parts of body, in the blood, and wherever it meets the H_2S which is formed in mouth and diffuses through the mucosa, a ppt. of lead sulphide is formed. The obvious objection to this idea is that lead sulphide could hardly form if lead occurred in blood, as lead phosphate is a more insoluble salt. However, as H_2S accumulates from decaying matter in mouth, more lead must change from phosphate to sulphide in accordance with law of mass action. This would be greatly accelerated if the reaction of the tissues was more acid than that of blood, for in an even slightly acid medium, tertiary lead phosphate is gradually converted to the di-lead salt which is about 15 times more soluble than the sulphide.

There is evidence that the changes also occur in the gums before the lead line is grossly visible. In the human and in cats, distinct localized hyperemia has been seen to precede the lead line. In this condition the gums are sore and bleed easily. The redness, merely inflammatory reaction to foreign particles of lead sulphide precipitated in tissue, can be seen microscopically and it may be concluded that the deposition of lead salts in the gums begins before lead line is grossly visible and that the discoloration is evident only after the deposit becomes sufficiently great. The possibility of an interrelation between the lead line and caries of the teeth is also important. It was found that lead is deposited directly in the teeth just as in other bones, and it is thought that this might be the cause of caries. The notoriously poor teeth of lead workers seem to indicate that the deposition of lead in teeth may be important in causing decay. It might be thought, however, that carries in teeth of workmen is due to their unhygienic habits rather than action of lead.

Lead Colic.

As to lead colic, though not in itself of serious consequence, it is the most painful and dreaded symptom of lead poisoning and presents a difficult diagnostic problem. The physiological mechanisms as yet are very little understood because of scarcity of experimental data, but it is generally agreed that any condition of colic is due to marked spasm of small intestine. Various explanations of the exact mechanism by which lead causes this spasm of intestine fall into two groups:

(a) Lead may act on one of the nervous structures supplying the intestines.

(b) It may directly affect smooth muscle itself.

If colic is due to muscular contraction, then it must be either (a) stimulation of vagus, through its center in medulla, the nerve itself, or its ending; (b) the inhibition of some part of sympathetic nervous system, or (c) stimulation of the muscle directly.

Wasserman poisoned cats with lead and examined gastro-intestinal tract by X-ray. He found hyper-mobility of small intestine and broadening of its contents with disappearance of usual beaded picture—suggesting a loss of tone. In the large intestine contraction rings and peristalsis were marked and this was accompanied by delay in excretion of contents. He thought the colic was apparently associated with spasm of small rather than of the large intestine and that during attacks, the small intestine is contracted to size of a thread.

Wasserman attributes colic to sclerosis of the sympathetic ganglia and believes this would permit unopposed vagus activity to cause intestinal spasm.

But Hanzlik tried an ingenious experiment on ducks. By inserting a small rubber balloon into the crop, he was able to record perstaltic contractions on a kymograph They were more vigorous, rapid and regular in lead poisoned ducks and neither atropine nor epinephrin affected them, but chiledonin, which depresses smooth muscle independently of nerve endings, promptly inhibited the contractions. He therefore concludes that augmentation of contraction due to lead was caused by direct stimulation of smooth muscle.

Also from experiment by Sucarde and Dozzi with isolated smooth muscle from gastro-intestinal tract, uterus, blood vessels, and ureters, we are led to believe that lead acts to a great extent on muscle fibre and not on nerves alone.

The outstanding result of Seccarde's experiments was the finding that lead inhibits the spontaneous contractions and increases the tonicity of the smooth muscle.

As yet sufficient data for a definite physiological explanation of lead colic have not been collected, but it is apparent that lead does not exercise a selective action on any of the nervous structures of the gastro-intestinal tract, and the most reasonable suggestion to explain lead colic is that the lead acts directly on the smooth muscle of intestine—producing increased tone and loss of mobility.

Lead Palsy.

The action of lead on an isolated nerve has been studied in the laboratory. As judged by muscular response the conductivity of the "leaded nerve" was exactly the same as that of the control even after exposure to concentrations as high as 0.46 mgm. per cc. —the largest quantity soluble in Ringer's Solution of pH. 6.5. Therefore as far as such experiment can determine lead produces no decrement in nerve conduction. To check results an attempt was made to determine by the string galvanometer the action currents of both nerve and muscle as a delicate index of function. In one part of the nerve-muscle preparations, the nerve was exposed to lead, in the other, the muscle. One experiment demonstrated quite distinctly that after fatigue the action current of "leaded" muscle diminished rapidly and soon disappeared entirely, while that of control muscle returned to normal within a short time and persisted to the end of experiment. Similar undiminished action currents were obtained from both normal and "leaded" nerves. Thus, the distinct inhibitory action of lead on isolated muscle and lack of deleterious action on nerve is confirmed.

From various other considerations which are too numerous to touch upon, a possible explanation of lead palsy has been arrived at. Lead is transported by the blood as an insoluble phosphate in colloidal state. In regions of muscular activity this is dissolved by the excess of lactic acid which diffuses from fatigued muscle cells and is converted into lead lactate. As sol. lactate comes in contact with inorganic phosphate at the surface of muscle cells, lead is precipitated as insol. phosphate. The reaction depends upon relative concentrations of lactate and phosphate. This suggests that the physiological lesions of lead palsy is in the muscle itself and that those muscles which are fatigued are most susceptible to lead paralysis Furthermore, it suggests that susceptibility to lead palsy depends on the chemical reaction between lead and the metabolic products formed during muscular activity.

Encephalopathy.

In conclusion, let us just touch upon perhaps the most dramatic manifestation of lead poisoning,—the development of acute mental changes. A condition described as encephalopathy. Carnus has studied lead encephalopathy experimentally by injecting lead into the subarachnoid space of a dog. Within 2 or 3 days symptoms of encephalopathy result, — excitability, hallucinations, and convulsions just before death. If he injected lead directly into the brain substance, no symptoms developed and only necrosis of small areas of the brain resulted. Neither did the mere administration of lead intravenously produce any mental symptoms. According to Carnus, lead is transported as particles of lead albuminate by the leucocytes and is excreted in the meninges when they are irritated or defective. But since lead is carried in the blood as the phosphate in colloidal sol. this theory is incorrect. However, Carnus' experimental observations are nevertheless exceedingly important because they demonstrate the relation between mental manifestations of lead poisoning and the pathological functioning of the meninges. They would indicate that in so-called lead encephalopathy, the meninges are primarily involve and the disease is really meningopathy.

Conclusion.

Apparently the basic element in all manifestations of lead poisoning is the carrying of lead by the blood as a phosphate in colloidal state, it being carried to the various situation in the body by the body fluid and there bringing about various physiological reactions producing the symptoms of plumbism just discussed.

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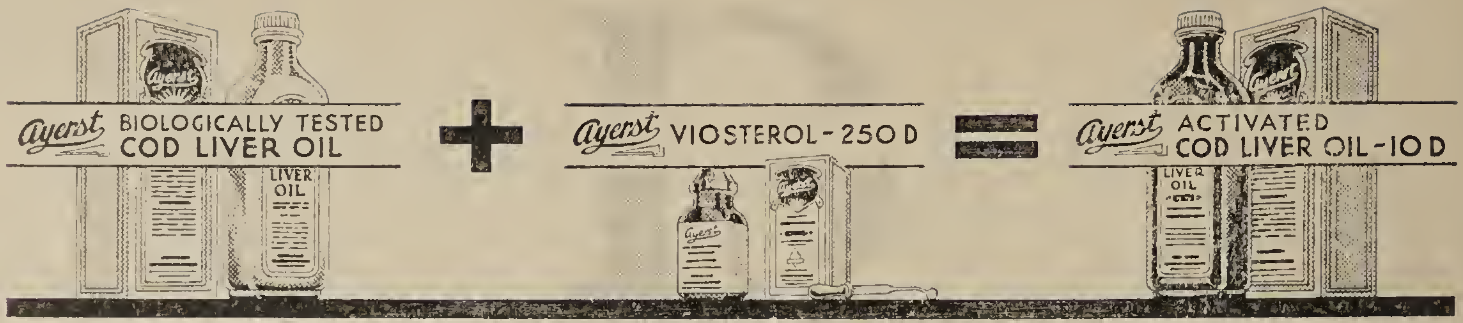
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